NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

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NewsScan

NIDA ADDICTION RESEARCH NEWS

NEWS UPDATE

Research News

Real-Time Monitoring of Dopamine Activity in Brain Helps Explain How Environmental Cues Contribute to Cocaine Relapse

Real-time monitoring of dopamine activity in the brain shows that in rats the mere anticipation of receiving cocaine may cause significant increases in dopamine levels. This finding may help explain why, in humans recovering from cocaine addiction, cocaine paraphernalia, surroundings, and other factors associated with drug use can elicit an intense craving for the drug, often resulting in relapse to use. Dopamine is a brain chemical associated with feelings of pleasure (reward); increases in dopamine levels in an area of the brain called the nucleus accumbens have been associated with drug use. Measuring dopamine level changes in real time enable researchers to carefully and accurately correlate drug-related behaviors in rats with changes in brain chemistry.

The researchers trained male rats to self-administer cocaine by pressing a lever and to associate the availability of cocaine with certain cues such as changes in lighting and an auditory tone. During daily sessions, the rats had access to cocaine and their behavior was recorded. Using fast-scan cyclic voltammetry, the researchers monitored changes in dopamine levels in the nucleus accumbens of the rats every 100 milliseconds while the rats had access to cocaine or were exposed to drug-related cues. Voltammetry allows subsecond measurements of dopamine release by monitoring changes in electrochemical currents that occur when brain cells release dopamine.

In the seconds following the cues, but before rats pressed the lever to receive cocaine, researchers observed an increase in dopamine in rats' brains. After each lever press, an additional increase in dopamine was measured.

In another experiment, the researchers found that they could initiate drug-seeking behaviors in rats by stimulating the release of dopamine in the nucleus accumbens.

- **WHAT IT MEANS:** These findings reveal for the first time that rapid dopamine transmission occurs during key components of cocaine-seeking behavior and during presentation of cocaine-associated stimuli.

This study, published by Dr. Regina Carelli and colleagues from the University of North Carolina at Chapel Hill and funded by the National Institute on Drug Abuse, appeared in the April 10 issue of *Nature*.

Starting Marijuana Use in Mid-Teens or Younger May Result in Cognitive Impairment Later in Life But Reasons are Unclear

There is evidence that individuals who start to smoke marijuana at an early age—while the brain is still developing—show deficits in cognition which are not seen in individuals who begin use of the drug when they are older. The reasons for this difference are unclear.

Scientists from the Harvard Medical School and from the intramural research program of the National Institute on Drug Abuse (NIDA) found lasting cognitive deficits in those who started to smoke marijuana before age 17. The researchers analyzed neuropsychological test results from 122 long-term heavy users of marijuana and 87 subjects who had used marijuana only a few times (control subjects). Sixty-nine of the 122 users started using marijuana at age 17 or before. The subjects were between the ages of 30 and 55 at the time of the study, and all had refrained from any drug use 28 days prior to testing.

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Individuals who started using marijuana at age 17 or younger performed significantly worse on the tests assessing verbal functions such as verbal IQ and memory of word lists than did those who started using marijuana later in life or who had used the drug sparingly. There were virtually no differences in test results among the individuals who started marijuana use after age 17 and the control subjects.

The investigators suggest three possible hypotheses that might explain these differences. One possibility is that early-onset smokers had lower innate cognitive skills before they ever started smoking marijuana. A second possibility is poor learning of certain cognitive skills by young users of marijuana who neglect school and academic pursuits. The third and most ominous possibility is that marijuana itself has a neurotoxic effect on the developing brain. According to the authors, further research will be required to determine the relative contributions of these three factors.

- **WHAT IT MEANS:** Youth who use marijuana before their midteens may show long-term deficits in certain verbal skills—but the reasons for these deficits are not yet clear.

Dr. Harrison Pope and colleagues published the study in the March 2003 issue of the journal *Drug and Alcohol Dependence*.

Study Finds Lobeline Reduces Self-Administration of Methamphetamine in Rats

Lobeline, a drug with a long history of use in smoking cessation programs, may be a potential treatment for methamphetamine abuse. In a previous study using rats, researchers from the University of Kentucky found that lobeline decreased the animals' self-administration of d-methamphetamine (METH). They concluded that lobeline acted by decreasing the animal's perception of METH- induced pleasure (reward).

The researchers conducted a series of experiments with male rats that were trained to self-administer METH by pressing a lever. In a group of rats that consistently self-administered METH, the researchers exchanged METH with lobeline to determine whether lobeline would serve as a substitute for METH. When METH was exchanged with lobeline, the number of times the rats pressed the lever decreased daily over the course of the experiment, indicating that lobeline did not serve as substitute for METH.

In a different experiment, the researchers investigated whether lobeline would cause rats to resume drug-seeking behavior after a period of abstinence or if it alters METH-induced reinstatement of drug-seeking behavior. They found that lobeline did not restore drug-seeking behavior nor did it alter METH-induced reinstatement. These findings indicate that lobeline appears to alter the mechanisms mediating METH reward, but not the mechanisms mediating the reinstatement of drug-seeking behavior.

In another experiment, the effects of lobeline on dopamine levels in the brains of rats were examined. It was found that lobeline had no effect on dopamine levels, the brain chemical that regulates feelings of pleasure. This finding indicates that lobeline does not induce the same feelings of reward as METH and that lobeline did not act as a substitute reinforcer. This finding would indicate that lobeline, unlike some other pharmacological agents used to treat addiction, does not itself pose a risk for abuse.

- **WHAT IT MEANS:** The ability of lobeline to decrease METH self-administration without inducing reward itself suggests that lobeline may be a useful pharmacological treatment without risk of abuse.

Dr. Steven Harrod and colleagues published the study in the February 23 issue of the journal *Psychopharmacology*.

Sigma Receptors Play Role in Cocaine-Induced Suppression of Immune System

Cocaine use is known to have negative effects on the immune system but how the drug exerts this effect is poorly understood. Now a research team, led by Dr. Steven Dubinett from the University of California Los Angeles Lung Cancer Research Program, has demonstrated that some of cocaine's effects on the immune system may be mediated by sigma receptors. These receptors are unique proteins found in the brain and other areas of the body and have been shown to play a role in some of the toxic and behavioral effects of the drug.

The researchers administered cocaine or saline to male mice five times per week. Another group of mice were given the sigma receptor antagonist BD1047—a substance that blocks the sigma receptors and does not stimulate them—in addition to cocaine or saline. After 2 weeks, tumor cells were implanted in the mice. Tumor growth and interleukin (IL)-10 concentrations were measured. IL-10 is a chemical messenger that suppresses the production of

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several substances that inhibit tumor growth. Tumors in cocaine-exposed mice were significantly larger and contained higher levels of IL-10 than those in saline-treated mice. However, tumor growth was less enhanced in mice who received both cocaine and treatment with the sigma receptor antagonist BD1047. In addition, administration of anti-IL-10 antibody reversed the tumor growth-promoting effects of sigma ligand agonists—substances that bind to and stimulate the receptors—such as cocaine.

In a separate study, the researchers administered cocaine or saline and the sigma receptor antagonist BD1047 to male mice. Two weeks later, the mice were administered staphylococcal entertoxin, which promotes IL-10 production by immune cells. The researchers found that the level of IL-10 in the blood of cocaine-exposed mice was significantly higher than those receiving saline but IL-10 production was inhibited in mice who received the sigma receptor antagonists.

- **WHAT IT MEANS:** These finding suggest that cocaine and other drugs that stimulate sigma receptors may promote tumor growth by increasing the production of immunosuppressive chemical messengers.

This study, cofunded by the National Institute on Drug Abuse, was published in the April 1 issue of *The Journal of Immunology*.

Upcoming Events

Annual PRISM Awards Scheduled May 8 in Los Angeles

The **7th Annual PRISM Awards™** will be presented on Thursday, May 8, 2003, in Los Angeles. The telecast will air as a one-hour special on Sunday, May 25, on FX Networks. A highlight of this year's ceremony is a new category that recognizes individual performances in feature films, television series and made-for-TV movies.

The **7th Annual PRISM Awards**, are presented in partnership with the Entertainment Industries Council, Inc. (EIC), The Robert Wood Johnson Foundation (RWJF) and the National Institute on Drug Abuse(NIDA)/National Institutes of Health. The PRISM Awards are the entertainment industry's only annual awards ceremony honoring the accurate depiction of drug, alcohol, and tobacco use and addiction in movies, television, video, music, interactive, and comic book entertainment. Seventy-nine nominees were selected from among a total of 313 submissions—a record number of submissions for the Awards show.

For a complete list of nominees or more information about the PRISM Awards, consult the *PRISM Awards* Web site at **http://www.prismawards.com**.

NIDA to Host Symposium on May 14-15 Honoring the Late Dr. Roger Brown

NIDA will host a two-day symposium—**Foundations and Innovations in the Neuroscience of Addiction**—on Wednesday, May 14, and Thursday, May 15, 2003, to honor the late Dr. Roger Brown.

At the time of his death in June 2002, Dr. Brown was NIDA's associate director of neuroscience in the Division of Neuroscience and Behavioral Research. For more than 20 years he was instrumental in fostering the development of cutting-edge neuroscience research in the area of drug abuse and addiction. The programs he helped develop have made seminal contributions to the current understanding of neurobiological substrates for reinforcing effects of drugs of abuse, the transition to compulsive, uncontrollable patterns of use, and events that trigger relapse.

Nobel laureate Dr. Arvid Carlsson will deliver a keynote address. In addition, more than 20 prominent scientists studying motivation and reward, cognition, neurotoxicity, pain and analgesia, and neuroplasticity will highlight contemporary research findings.

The meeting will be held in the Natcher Auditorium on the campus of the National Institutes of Health, Bethesda, Maryland. More information will be posted on NIDA's Web site—**www.drugabuse.gov**—as it becomes available.

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For more information about any item in this *NewsScan*:

- **Reporters**, call **Michelle Person** at 301-443-6245.
- **Congressional staffers**, call **Mary Mayhew** at 301-443-6071.

The National Institute on Drug Abuse (NIDA) is a component of the National Institutes of Health, U.S. Department of Health and Human Services. NIDA supports more than 85 percent of the world's research on the health aspects of drug abuse and addiction. The Institute carries out a large variety of programs to ensure the rapid dissemination of research information and its implementation in policy and practice. Fact sheets on the health effects of drugs of abuse and other topics are available in English and Spanish. These fact sheets and further information on NIDA research and other activities can be found on the NIDA home page at **http://www.drugabuse.gov**.

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